

Appendix A

The Original Guidance with Tracked (highlighted) Editorial Suggestions

Guidance for Industry

Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**October 2003
Pharmaceutical CGMPs**

Guidance for Industry

Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Pharmaceutical Science (OPS)
Office of Compliance (OC)**

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist manufacturers of human drug products in meeting the requirements of 21 CFR 211.110 for demonstrating the adequacy of mixing to ensure uniformity of in-process powder blends and finished solid oral dosage units (*comment: please add more description here as to the general types of dosage units included. We assume this also includes wet granulations?*). ~~This guidance describes the procedures for assessing powder mix adequacy, correlating in-process dosage unit test results with powder mix test results, and establishing the initial criteria for control procedures used in routine manufacturing.~~ This guidance describes a control procedure for the manufacturer to routinely assess the adequacy of powder mix/drug uniformity by the use of stratified in-process dosage unit sampling and testing instead of routine blend sampling, provided that a feasibility assessment is made prior to implementation of the stratified sampling approach.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

¹ This guidance has been prepared by the Office of Pharmaceutical Science and the Office of Compliance in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration in cooperation with the Product Quality Research Institute (PQRI) (see footnote 3). This guidance document represents the Agency's current thinking on assessment of the uniformity of powder blends and finished dosage units in the absence of new technology development or implementation.

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37 II. BACKGROUND

38

39 This guidance is the result of an Agency effort to achieve a science-based policy and regulatory
40 enforcement. Experts from industry, academia, and the FDA developed the principles
41 underlying this guidance after extensive public discussion. A brief history of the evolution of
42 this guidance is provided in the following paragraphs.

43

44 In response to industry concerns regarding regulations for demonstrating the adequacy of in-
45 process powder mixing, the FDA published a draft guidance for industry containing new
46 approaches for a blend uniformity analysis in August 1999.² Comments submitted to the docket
47 resulted in the formation of the Blend Uniformity Working Group (BUWG) by the Product
48 Quality Research Institute (PQRI).³ The PQRI BUWG conducted a public meeting, PQRI
49 Workshop on Blend Uniformity, on September 7 and 8, 2000.

50

51 Using the consensus reached by participants in this workshop, the BUWG developed a draft
52 recommendation, *The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate*
53 *Adequacy of Mix for Powder Blends*. The draft recommendation received examination and peer
54 review in multiple scientific and public venues. In addition, the Advisory Committee for
55 Pharmaceutical Science (ACPS) reviewed the draft recommendation and received public
56 comment during scheduled meetings of the committee.⁴ The draft recommendation was revised
57 to incorporate the results of peer review and public comment and was presented to CDER's
58 Center Director in final form on December 30, 2002. The recommendation was subsequently
59 published in the *PDA Journal of Pharmaceutical Science and Technology*.⁵ This draft guidance
60 reflects CDER's effort to incorporate the draft recommendation into regulatory policy.

61

62

63 III. SCOPE

64

65 ~~Stratified sampling~~ Stratified sampling of dosage units is the a process of sampling dosage units
66 ~~at predefined intervals and collecting representative samples from specifically predefined,~~
67 targeted locations in the compression/filling operation dosage unit forming process that have the
68 greatest potential to yield extreme highs and lows in test results. These test results are used to
69 monitor the manufacturing process output ~~that is~~ from the locations most responsible for causing

² The FDA withdrew the guidance for industry *ANDAs: Blend Uniformity Analysis* on May 17, 2002.

³ PQRI is a collaborative body involving FDA's Center for Drug Evaluation and Research (CDER), industry, and academia. Since its inception in January 1996, the mission of PQRI has been to generate scientific information in support of regulatory policies through research. Additional information about PQRI is available at www.pqri.org.

⁴ The PQRI BUWG recommendation appeared on the public ACPS agenda on November 28, 2001 (introduction), May 8, 2002 (distribution and comment), and October 22, 2002 (final comment).

⁵ G Boehm, J Clark, J Dietrick, L Foust, T Garcia, M Gavini, L Gelber, J Geoffrey, J Hoblitzell, P Jimenez, G Mergen, F Muzzio, J Planchard, J Prescott, J Timmermans, and N Takiar, "The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Powder Blends, *PDA J. Pharm. Sci Technol.*, 57:59-74, 2003.

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70 finished product variability. ~~The test results~~ Stratified sampling of dosage units can be used to
71 ~~develop a single control procedure to ensure adequate powder mix and in some cases,~~ uniform
72 content in finished products.

73
74 The methods described in this guidance are not intended to be the only methods for meeting
75 Agency requirements to demonstrate the adequacy of powder mix. Traditional powder blend
76 sampling and testing, in conjunction with testing for uniformity of content in the finished
77 product, can be used to comply with current good manufacturing practice requirements
78 (CGMPs). Use of at-, in-, or on-line measurement systems can also be appropriate and are
79 described in other guidance documents.⁶ After readily passing (Section V.B.2) the validation
80 requirements, products that are allowed to meet USP Uniformity of Dosage Units by weight
81 variation are exempted from future routine blend testing requirements.

82
83 This guidance provides recommendations on how to:

- 84
- 85 • Conduct powder blend sampling and analyses.
- 86 • Establish initial criteria for stratified sampling of in-process dosage units⁷ and evaluation
87 of test results.
- 88 • Analyze the stratified samples and evaluate data.
- 89 • ~~Correlate-Compare~~ Compare the stratified sample data with the powder blend data.
- 90 • Assess powder mix uniformity.
- 91 • ~~Correlate-Compare~~ Compare the stratified in-process dosage unit sample data with the finished
92 dosage unit data ~~and assess to determine whether in-process samples may be used to~~
93 assess uniformity of content.
- 94 • Test exhibit and validation batches for adequacy of powder mix.
- 95 • Test and evaluate routine manufacturing batches.
- 96 • Report the use of stratified sampling in the application.

97
98 The methods described in this guidance can be used to monitor active ingredient homogeneity of
99 powder blends and to ensure uniform content of the finished product for solid oral drug products.
100 These methods are only one way to satisfy the CGMP and application review requirements for
101 in-process testing to demonstrate adequacy of powder mix and uniform content of the finished
102 product. The method assumes appropriate monitoring of all manufacturing steps as required by
103 the regulations or application commitments. This guidance does not discuss the assessment of
104 the potency and other attributes that can affect the finished dosage units, or the homogeneity of

⁶ In ~~August-September~~ 2003, the Agency issued the draft guidance for industry *PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance*. Once finalized, it will represent the Agency's perspective on this issue.

⁷ The in-process dosage unit is a capsule or tablet as it is formed in the manufacturing process before it is coated or packaged.

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105 inactive ingredients. ~~Some formulations with extremely low dose and/or high potency may call~~
106 ~~for more rigorous sampling than that described in this guidance to assess the uniformity of~~
107 ~~powder blends or the uniformity of content of the finished dosage units.~~

108
109 When using the methods described in this guidance, ~~certain data or trends may be observed in~~
110 ~~the data.~~ We recommend that manufacturers scientifically evaluate ~~these types of research data~~
111 ~~for trends, to determine~~ if they affect the quality of a product and, if so, how. The FDA does
112 not intend to inspect research data collected on an existing product for the purpose of evaluating
113 the suitability of proposed methods. Any FDA decision to inspect research data would be based
114 on exceptional situations similar to those outlined in Compliance Policy Guide Sec. 130.300.⁸
115 Those data used to support validation or regulatory submissions will be subject to inspection in
116 the usual manner.

117 118 119 **IV. CORRELATION OF EVALUATION OF POWDER MIX AND IN-PROCESS** 120 **STRATIFIED SAMPLING DURING PROCESS DEVELOPMENT WITH POWDER MIX** 121 **AND FINISHED PRODUCT**

122
123 If you plan to follow the procedures described in this guidance document, we recommend that
124 you first complete the ~~process development procedure~~ evaluation described in this section before
125 using the methods described in sections V and VI, VII. The subsections below describe ~~how~~
126 ~~to the initial assessment of the adequacy of powder mix uniformity in the blend and, uniformity~~
127 ~~of content of the stratified in-process and finished dosage units through correlation and~~
128 ~~assessment evaluation of data from development, validation and manufacturing batch(es).~~ These
129 procedures can reveal deficiencies in the blending operation that may not ~~have been~~
130 ~~previously otherwise be~~ detected. We recommend that manufacturers correct deficiencies in the
131 blending operation before validation and implementation of the routine manufacturing control
132 methods described in this guidance.

133 134 **A. Assessment of Powder Mix Uniformity**

135
136 As part of development, we recommend that you assess critical events in the blending process
137 and determine appropriate sampling techniques for demonstrating a validated blend process. As
138 part of this evaluation, we recommend the assessment of powder mix uniformity using the
139 following procedures:

- 140
141 • Conduct blend analysis on batches by ~~extensively~~ sampling the mix in the blender⁹ and/or
142 intermediate bulk containers (IBCs). When sampling from a blender, identify sampling
143 locations¹⁰ to represent potential areas of poor blending. For example, in tumbling

⁸ FDA/ORA Compliance Policy Guide, Sec. 130.300, *FDA Access to Results of Quality Assurance Program Audits and Inspections* (CPG7151.02)

⁹ Sampling can be done from other equipment that is being used to mix the blend, such as a fluid bed.

¹⁰ Typically, at least 10 locations for tumbling blenders and at least 20 locations for convective blenders are selected.

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144 blenders such as V-blenders, double cones, or drum mixers, samples should be selected
145 from at least two depths along the axis of the blender. For convective blenders such as a
146 ribbon blender, a special effort should be made to implement uniform volumetric
147 sampling to include the corners and discharge area.

148 • Identify appropriate blending time and speed ranges, dead spots in blenders, and locations
149 of segregation in IBCs. ~~Determine sampling errors.~~

150 • Define the effects of sample size-quantity (e.g., 1-10X dosage unit range) while
151 developing a technique capable of measuring the true uniformity of the blend. Sample
152 quantities larger than 3X can be used with adequate scientific justification. Appropriate
153 blend sampling techniques and procedures should be developed for each product with
154 consideration to various designs of blend powder sampling and the physical and chemical
155 properties of the blend components.

156 ~~□ Design blend sampling plans and evaluate them using appropriate statistical analyses.~~

157 • ~~Quantitatively measure and~~ evaluate the variability that is present among the samples.
158 Attribute the sample variability to either lack of uniformity of the blend or sampling
159 error. ~~Significant-High~~ within-location variance in the blend data can be an indication of
160 one factor or a combination of factors such as inadequacy of blend mix, sampling error,¹¹
161 analytical error, or agglomeration.^{12, 13} ~~Significant-High~~ between-location variance in the
162 blend data can indicate that the blending operation is inadequate.

163 • Based upon the results of the development work, identify a sampling and testing plan
164 appropriate for validation of powder mix uniformity (e.g., sampling locations, sample
165 quantity, appropriate statistical analyses).

166

167 **B. ~~Correlation-Evaluation of Powder Mix Uniformity with~~ using Stratified In-** 168 **Process Dosage Unit Data**

169

170 As part of development, we recommend that you assess the in-process dosage unit data to
171 identify locations throughout the forming operation that have a higher risk of producing failing
172 finished product uniformity of content results due to segregation or poor powder mix. We
173 recommend the following steps for correlation:

174

¹¹ If blend sampling error is detected, more sophisticated, statistical analyses should be applied to assess the situation, such as the use of methods described in J Berman, DE Elinski, CR Gonzales, JD Hofer, PJ Jimenez, JA Planchard, RJ Tlachac, PF Vogel, "Blend Uniformity Analysis: Validation and In-Process Testing." *Technical Report No. 25, PDA J Pharm. Sci. Technol.* 51(Suppl 3i-iii), S1-99, 1997.

¹² OS Sudah, PE Arratia, D. Coffin-Beach, FJ Muzzio, "Mixing of Cohesive Pharmaceutical Formulations in Tote (Bin)-Blenders," *Drug Dev. Ind. Pharm*, 28(8): 905-918, 2002.

¹³ V Swaminathan, DO Kildsig, "Polydisperse powder mixtures: effect of particle size and shape on mixture stability," *Drug Dev. Ind. Pharm.*, 28(1):41-48, 2002.

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- 175 • Conduct periodic sampling and testing of the in-process dosage units by sampling them at
176 defined intervals ~~and locations~~ throughout the compression or filling process. ~~Use a~~A
177 minimum of 20 appropriately spaced in-process dosage unit sampling points is
178 recommended. There should be at least 7 samples taken¹⁴ from each of these locations
179 for a total minimum of at least 140 samples.
- 180 • Take at least 7 samples from each additional location to further assess each significant
181 event,¹⁵ such as filling or emptying of hoppers and IBCs, start and end of the
182 compression or filling process and equipment shutdown. ~~This may be accomplished by~~
183 ~~using process development batches, validation batches, or by using routine manufacturing~~
184 ~~batches for approved products.~~
- 185 • Significant events may also include observations or changes from one batch to another
186 (e.g., batch scale-up and observations of undesirable trends in previous batch data).
- 187 • ~~-Prepare a summary of the data (and analysis), identifying the significant events observed~~
188 ~~in the manufacturing process that may impact blend uniformity. From this, identify 20~~
189 ~~stratified sampling locations that may be used to verify or validate blend uniformity¹⁶.~~
190 ~~used to correlate the stratified sampling locations with significant events in the blending~~
191 ~~process. We recommend you submit this summary with the application as described in~~
192 ~~section VIII of this guidance.~~
- 193 • Compare the powder mix uniformity data with the in-process dosage-unit uniformity data
194 described above.
- 195 • Investigate any discrepancies observed between powder mix and dosage-unit data and
196 establish root causes. At least one trouble-shooting guide is available that may be helpful
197 with this task.¹⁷ Possible corrections may range from going back to formulation
198 development to improve powder characteristics to process optimization. Sampling
199 problems may also be ~~negated~~ obviated by use of alternate state-of-the-art methods of in
200 situ real-time sampling and analysis (e.g., P.A.T.).

201

~~C. Correlation of Stratified In-Process Samples with the Finished Product~~

202

203

204

205

We recommend the following steps:

¹⁴ A minimum of 3 (of the 7) dosage units per location should be assayed.

¹⁵ A *significant event* is any operation during the solid dosage production process that can affect the integrity of the in-process materials – see section IX Glossary.

¹⁶ Validation of blend uniformity should include both the verification of adequate powder mix and of adequate blend uniformity in the dosage units.

¹⁷ JK Prescott, TJ Garcia, "A Solid Dosage and Blend Content Uniformity Troubleshooting Diagram," Pharm. Technol., 25 (3):68-88, 2001.

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- 206 ~~□ Conduct testing for uniform content of the finished product using an appropriate procedure~~
207 ~~or as specified in the Abbreviated New Drug Application (ANDA) or the New Drug~~
208 ~~Application (NDA) for approved products.~~
- 209 ~~□ Compare the results of stratified in-process dosage unit analysis with uniform content of~~
210 ~~the finished dosage units from the previous step. This analysis should be done without~~
211 ~~weight correction.⁺⁸~~
- 212 ~~□ Prepare a summary of the data and analysis used to conclude that the stratified in-process~~
213 ~~sampling provides assurance of uniform content of the finished product. We recommend~~
214 ~~you submit this summary with the application as described in section VIII of this~~
215 ~~guidance.~~

V. EVALUATION OF EXHIBIT/VALIDATION BATCH POWDER MIX HOMOGENEITY

222 ~~This section describes sampling and testing the powder mix of exhibit and process validation~~
223 ~~batches used to support implementing the stratified sampling method described in this guidance.~~
224

225 We recommend that during the manufacture of exhibit and process validation batches, you assess
226 the uniformity of the powder blend, and the in-process dosage units, and the finished product to
227 ensure adequacy of blend uniformity independently. ~~We recommend you use the following steps~~
228 ~~to identify sampling locations and acceptance criteria prior to the manufacture of the exhibit~~
229 ~~and/or validation batches. We recommend that sampling locations for blend and stratified~~
230 samples should be identified per Section IV. This comparison of powder mix uniformity and
231 stratified in-process dosage unit uniformity is completed before establishing the criteria and
232 controls for routine manufacturing.
233

A. Demonstrating Powder Mix Uniformity

236 This section describes sampling and testing the powder mix of exhibit and process validation
237 batches used to support implementing the stratified sampling method described in this guidance.
238 Some powder blends may present unacceptable safety risk or be physically impractical (e.g.,
239 large V-blender) when directly sampled. Once described, these situations may justify an
240 alternate procedure. In such cases, process knowledge and data from indirect sampling
241 combined with additional in-process dosage unit data may be adequate to demonstrate the
242 adequacy of the powder mix. Data analysis used to justify using these alternate procedures
243 should be described in a summary report that is maintained at the manufacturing facility. In
244 general, we recommend:
245

¹⁸ Weight correction is a mathematical correction to eliminate the effect of potentially variable ~~tablet dosage unit~~ weight on measurement of mix adequacy—see Glossary, Section IX.

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246 1. ~~Carefully identify at least 10 sampling locations in the blender to represent potential areas~~
247 ~~of poor blending.~~ Identify at least 10 locations to collect powder blend samples. If taken
248 from the blender, they should include areas that may be problematic in terms of uniform
249 blend¹⁹. For example, in tumbling blenders (such as V-blenders, double cones, or drum
250 mixers), samples should be selected from at least two depths along the axis of the
251 blender. For convective blenders (such as a ribbon blender), a special effort should be
252 made to implement uniform volumetric sampling to include the corners and discharge
253 area (at least 20 locations are recommended to adequately validate convective blenders).

254
255 2. Collect at least 3 replicate samples from each location. Samples should meet the
256 following criteria:

257
258 3. Assay one sample per location, with the number of samples (n) ≥ 10. (n ≥ 20 for
259 convective blender). Samples should meet the following criteria:

260
261 ~~Assay one sample per location (number of samples (n) ≥ 10)~~
262 ~~(n = 20 for ribbon blender).~~

- 263
- 264 • RSD (*relative standard deviation*) of all individual results ≤ 5.0 percent.
- 265
- 266 • All individual results are within 10.0 percent (absolute) of the mean of the results.
- 267

268 If samples do not meet these criteria, we recommend that you investigate the failure according to
269 the flow chart in Attachment 1. ~~We also recommend that you not proceed any further with~~
270 ~~implementation of the methods described in this guidance until the criteria are met.~~ Assay the
271 remaining replicate blend samples. To aid in investigating the cause of failure, dosage form
272 samples (7 from at least 20 locations) may be analyzed. These samples should have been
273 obtained following the procedure described below in Section V.B. If the cause of failure is
274 identified as a mixing problem, we recommend that you do not proceed further with
275 implementation of the methods described in this guidance until a new mixing procedure is
276 developed. If the cause of failure is not because of mixing, but is attributed to sampling error or
277 other problem(s) unrelated to the homogeneity of the blend, we recommend that you proceed
278 with the evaluation of the dosage form data as described in Section V.B (see also Attachment 1).

279
280 ~~Sampling errors may occur in some powder blends, sampling devices, and techniques that make~~
281 ~~it impractical to evaluate adequacy of mix using only the blend data. In such cases, we~~
282 ~~recommend that you use in-process dosage unit data in conjunction with blend sample data to~~
283 ~~evaluate blend uniformity.~~

284
285 ~~Some powder blends may present unacceptable safety risk when directly sampled. The safety~~
286 ~~risk, once described, may justify an alternate procedure. In such cases, process knowledge and~~
287 ~~data from indirect sampling combined with additional in-process dosage unit data may be~~

¹⁹ ~~This~~ Developing an appropriate sampling and testing plan is described in Section IV.A of this guidance.

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adequate to demonstrate the adequacy of the powder mix. Data analysis used to justify using these alternate procedures should be described in a summary report that is maintained at the manufacturing facility.

As an alternative, you can substitute the procedures described in the PDA Technical Report No. 25, (see reference in footnote 118) to ensure that the blend is uniform and that the method meets or exceeds the criteria described above.

B. Assessment and Classification of Stratified In-Process Dosage Unit Uniformity

VI. VERIFICATION OF MANUFACTURING CRITERIA

You should complete the assessment of powder mix uniformity and correlation of stratified in-process dosage unit sampling development procedures before establishing the criteria and controls for routine manufacturing. This section describes the sampling, testing, and evaluation of in-process dosage units collected using stratified sampling. These exhibit and process validation batch data are used to support implementing the stratified sampling method described in this guidance. We also recommend that you assess the normality and determine RSD from the results of stratified in-process dosage unit sampling and testing that were developed. The RSD value should be used to The manufacturing process will be classified the testing results as either *readily pass* (all batches have an RSD \leq 4.0%), *marginally pass* (all batches have an RSD \leq 6.0%) or *inappropriate* for demonstration of batch homogeneity (at least 1 batch has an RSD $>$ 6.0%). The procedures are discussed in the following sections:

1A. In-Process Dosage Unit Sampling and Analysis

We recommend the following steps:

- Carefully identify locations²⁰ throughout the compression or filling operation to sample in-process dosage units. The sampling locations should also include significant process events such as hopper changeover, filling or machine shutdown and the beginning and end of the compression or filling operation.²¹ There should be at least 20 locations with 7 samples each for a minimum total of 140 samples. These include periodic sampling locations and significant event locations.
- Sample at least 7 in-process dosage units from each sampling location.
- Assay at least 3 of the 7 and weight correct each result. (The number of samples should be specified and justified for a given product and process.) Assay all 7 per location if required in Section V.A.

²⁰ Prior identification of appropriate sampling locations is described in Section IV.B of this guidance.

²¹ The beginning and end samples are taken from dosage units that would normally be included in the batch.

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- 327 • Analyze the dosage units according to the flowchart in Attachment 1. Adequate Powder
328 Mix is demonstrated, if for each batch:
- 329 • RSD of all individuals is < 6.0%
- 330 • Each location mean is within 90.0% - 110.0% of target potency
- 331 • All individuals (not weight corrected) are within 75.0% and 125.0% of the target
332 potency
- 333 • ~~Conduct an analysis of the dosage unit stratified sampling data to demonstrate that the~~
334 ~~batch has a normal~~ assess the active ingredient distribution of active ingredient throughout
335 the batch (e.g., visual assessment of a histogram or a probability plot). Indications of
336 trends, bimodal distributions, or other forms of a distribution other than normal-bell-
337 shaped should be investigated/evaluated. If these occurrences significantly affect your
338 ability to ensure batch homogeneity, they should be corrected.
- 339 • Prepare a summary of this analysis. Potential investigation results along with a
340 description of batch normality distribution should be included in the summary. Submit
341 this summary with the application as described in section VIII of this guidance.

2. Classifying the Test Results

342
343 ~~In addition to this analysis of batch normality~~ Additionally, we recommend that you classify the
344 test results as *readily pass* or *marginally pass* according to the following procedure:

B. Criteria to Meet the *Readily Pass* Classification

345
346 For each separate batch, compare the weight corrected test results to the following criteria:

- 347
- 348 • For all individual results (for each batch $n \geq 60$) the $RSD \leq 4.0$ percent.
- 349
- 350 • Each location mean is within 90.0 percent to 110.0 percent of ~~target strength~~ target
351 potency.
- 352
- 353 • All individual results without weight correction are within the range of 75.0 percent to
354 125.0 percent of ~~target strength~~ target potency.
- 355
- 356
- 357
- 358
- 359

360 If your test results meet these criteria for all batches, they are classified as *readily pass* and you
361 can start routine batch testing using the Standard ~~Verification~~ Criteria Method (SCVM)
362 described in section VII. If your test results for any of the batches fail to meet these criteria, you
363 may choose to test additional location samples and include these results to compare to *readily*
364 *pass* criteria. Alternatively, we recommend that you may compare the results to with the
365 *marginally pass* criteria described below with or without including additional test results.

366

C. Criteria to Meet the *Marginally Pass* Classification

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369 If your dosage unit test results fail to meet the criteria for the *readily pass* classification, you
370 should ~~assay the remaining dosage units (all 7 units per location) and compare the weight-~~
371 corrected test results to the following criteria:

372

373 • For all individual results (for ~~each~~one batch $n \geq 60$ ~~140~~) the $RSD \leq 6.0$ percent.

374

375 • Each location mean is within 90.0 percent to 110.0 percent of ~~target strength~~target
376 potency.

377

378 • All individual results without weight correction are within the range of 75.0 percent to
379 125.0 percent of ~~target strength~~target potency.

380

381 If your test results meet these criteria, results can be classified as *marginally pass*. If your
382 samples do not meet these criteria, we recommend that you investigate the failure, find justified
383 and assignable cause(s), correct the deficiencies, and if appropriate, repeat the powder mix
384 homogeneity assessment, in-process dosage unit sampling ~~correlation~~comparison, and initial
385 criteria establishment procedures. The disposition of batches that have failed the *marginally*
386 *pass* criteria is outside the scope of this guidance.

387

388 **C. Establish the Relationship Between Stratified In-Process Samples and the** 389 **Finished Product**

390

391 In order to use in-process samples to fulfill the compendial uniformity of dosage units
392 requirement for finished products, we recommend the following steps (this does not need
393 repeated, if the comparison was performed during development):

394

395 • Conduct testing for uniform content of the finished product using an appropriate
396 procedure or as specified in the Abbreviated New Drug Application (ANDA) or the New
397 Drug Application (NDA) for approved products.

398 • Compare the results of stratified in-process dosage unit analysis with uniform content of
399 the finished dosage units from the previous step. This analysis should be done without
400 weight correction.²²

401 • Prepare a summary of the data and analysis. If the stratified in-process data provides
402 assurance of uniform content of the finished product, then the in-process data may be
403 routinely used to demonstrate both uniformity of blend and final product content. See
404 section VII of this guidance for reporting requirements.

405 • If the in-process samples cannot be used to assure uniformity of dosage units, then the
406 compendial test on the final product will need to be continued in addition to in-process
407 stratified testing for blend uniformity.

²² Weight correction is a mathematical correction to eliminate the effect of potentially variable tablet dosage unit weight on measurement of mix adequacy—see Glossary, Section IX.

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D. Sample Locations for Routine Manufacturing

We recommend that you prepare a summary of the data analysis from the powder mix assessment and stratified sample testing. From the data analysis, you should establish the stratified sample locations for routine manufacturing, taking into account significant process events and their effect on in-process dosage unit and finished dosage unit quality attributes. You should identify ~~at least~~ 10 sampling locations (or more) during capsule filling or tablet compression to represent the entire routine manufacturing batch.

VII. ROUTINE MANUFACTURING BATCH TESTING METHODS

We recommend that you evaluate ~~the~~ routine manufacturing batches using in-process stratified samples against the following criteria, after completing the procedures described above to assess the adequacy of the powder mix and uniform content in finished dosage form.

These routine manufacturing batch-testing methods include the Standard Criteria Method (SCM) and the Marginal Criteria Method (MCM). The SCM consists of two stages, each with the same *accept/reject* criteria. The second of the two stages recommends using a larger sample size to meet these criteria. The MCM uses *accept/reject* criteria that are different from the SCM.

If the batch data fail to conform to the SCM criteria, we recommend continued sampling and testing to intensified criteria (MCM). Both verification methods and the procedures for switching from one to the other are detailed below and in the flow chart in Attachment 2.

A. Standard Criteria Method (SCM)

We recommend using the SCM ~~verification method~~ when ~~either~~ any of the following conditions ~~are~~ met:

- Results of establishing initial criteria are classified as readily pass and no previous batch failed SCM criteria.
- Previous routine batch was appropriately evaluated using SCM and met SCM criteria.
- Results of testing the previous routine batches using ~~to~~ the MCM pass the criteria for switching to the SCM (see section C below).

The SCM should meet the same criteria using a different number of sample test results as described below:

1. Stage 1 Test

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453 To perform the stage 1 test, we recommend that you (1) collect at least 3 dosage units from each
454 sampling location, (2) assay 1 dosage unit from each location, (3) weight correct the results, and
455 (4) compare the results with the following criteria:

456

457 • RSD of all individual results ($n \geq 10$) ≤ 5.0 percent.

458

459 • Mean of all results is 90.0 percent to 110.0 percent of target assay.

460

461 If your results pass these criteria, the adequacy of mix for the batch is adequate and you can use
462 stage 1 of SCM for the next batch. If the results pass these criteria and the adequacy of mix and
463 uniformity of dosage unit content for the batch are adequate, you can use the SCM for the next
464 batch. If test results fail stage 1 criteria, you should conduct extended testing to stage 2
465 acceptance criteria.

466

467 2. Stage 2 Test

468

469 To perform the stage 2 test, we recommend that you assay and weight correct the remaining two
470 dosage units (from stage 1) for each sampling location, and compute the mean and RSD of
471 data combined from both stage 1 and stage 2. Compare the results with the following criteria:

472

473 • For all individual results ($n \geq 30$) the RSD ≤ 5.0 percent.

474

475 • Mean of all results is 90.0 percent to 110.0 percent of target assay.

476

477 If your results pass these criteria, the adequacy of mix and uniformity of content for the batch are
478 is adequate and you can use stage 1 of SCM for the next batch. If test results fail the criteria, use
479 the MCM described in the next section.

480

481 B. Marginal Criteria Method (MCM)

482

483 We recommend using the MCM After powder mix assessment, in-process dosage unit stratified
484 sampling correlation and initial criteria establishment, we recommend that you use the MCM
485 when any either of the following conditions are met:

486

487 • Results of initial criteria establishment qualified as *marginally pass*.

488

489 • Previous routine batch was appropriately evaluated using MCM and met MCM criteria.

490

491 • ~~Results of initial criteria establishment qualified as *readily pass* or a~~ The current routine
492 batch was tested according to SCM and the test results failed both stage 1 and stage 2
493 criteria.

494

495 • Previous batch was first tested using SCM, but had to switch to MCM to pass.

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497 To perform the MCM test, we recommend that you (1) have assayed at least 3 dosage units from
498 each sampling location, (2) weight correct the results, and (3) compare the results with the
499 following criteria~~Then, we recommend you use~~ (note: the weight-corrected results from the
500 stage 2 SCM analysis and are compared to this with the MCM criteria if stage 2 SCM does not
501 pass):

- 502
- 503 • For all individual results ($n \geq 30$) the RSD ≤ 6.0 percent.
- 504
- 505 • Mean of all results is 90.0 percent to 110.0 percent of target assay.
- 506

507 We recommend that all results from analysis of any remaining location samples be computed
508 with the stage 2 SCM data. No test results should be removed from the analysis. If the test
509 results pass these criteria, the adequacy of mix ~~and uniformity of content~~ for the batch ~~are is~~
510 adequate, ~~and~~ and ~~we~~ recommend that you continue to test routine manufacturing batches with
511 MCM criteria. If the test results fail the criteria, you should no longer use the ~~verification~~
512 Routine Manufacturing Batch Testing Methods (Section VI) to ensure adequacy of mixing or
513 uniformity of content until you investigate the failure (per 21 CFR 211.192). That is, to establish
514 justified assignable cause(s), take necessary corrective actions, and if appropriate, repeat the
515 powder mix assessment, stratified sample correlation comparison, and initial criteria
516 establishment procedures. Or, adopt at, in, or on-line measurement systems to ensure adequate
517 powder mix assessment.

518

519 C. Switching to Standard Test Criteria Method from Marginal Test Criteria 520 Method

521

522 It is appropriate to switch to the SCM when the following criterion is met:

- 523
- 524 • Five consecutive batches pass the MCM criteria and ~~result in~~ for each batch the RSD \leq
525 5.0 percent
- 526
- 527

528 VIII. REPORTING THE USE OF STRATIFIED SAMPLING

529

530 A. Applications Not Yet Approved

531

532 This section refers to the scientific data analysis and other information that should be submitted
533 to an NDA or ANDA. Information submitted in the application should include summary reports
534 and scientific analyses or statements about the method being used. The raw data collected to
535 support using this method should be maintained at the manufacturing site.

536 We recommend that when available²³, you provide the following information in the
537 Manufacturing Process and Process Controls section of the application (CTD²⁴ 3.2.P.3.3).

²³ Sufficient data may not be available from full-scale batches at the time of the initial submission. If data summaries are not included in the application, they should be included in validation or development documents maintained at the site. Preliminary data at small-scale may be submitted, but the final analyses and comparisons should be performed on data from full-scale batches.

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- 538
- 539 • ~~Statement that the methods in this guidance are being used to demonstrate the adequacy~~
- 540 ~~of powder mix or a description of alternative methods that demonstrate the adequacy of~~
- 541 ~~the powder mix.~~ Method that will be used to demonstrate the adequacy of powder mix.
- 542 • Summary of data analysis from the powder mix assessment and from stratified sample
- 543 testing
- 544 • Summary of the in-process dosage unit stratified sampling data analysis ~~demonstrating a~~
- 545 ~~normal~~ evaluating the distribution of active ingredient in the batch
- 546 • Summary of the powder mix sampling data analysis demonstrating that it met the
- 547 minimum criteria for validation and establishing initial criteria
- 548

549 We recommend that you provide the following information in the Drug Product Specification

550 section of the application (CTD 3.2.P.4.1), if applicable:

551

- 552 • Statement in the product specification stating that the methods in this guidance are being
- 553 used to demonstrate finished product uniformity of content or a description of alternative
- 554 methods used to demonstrate finished product uniformity of content
- 555

556 We also recommend that you provide the following information in the Pharmaceutical

557 Development Information section of the application (CTD 3.2.P.2.2):

558

- 559 • Summary of data analysis for ~~correlation-comparison~~ of in-process dosage unit stratified
- 560 sampling with finished product uniformity of content
- 561
- 562 • Summary of data analysis for ~~correlation-comparison~~ of powder mix uniformity with in-
- 563 process dosage unit stratified sampling
- 564

565 B. Postapproval Change

566

567 If you plan on changing the existing controls for adequacy of mix and uniformity of content to

568 the methods described in this guidance, the change should be considered a minor change as

569 described in the postapproval changes guidance.²⁵ We recommend you provide a notice of the

570 change in the next annual report along with the information indicated in section A, above. The

571 raw data collected to support changes can be maintained at the manufacturing site.

572

²⁴ *M4Q: The CTD – Quality*, one in a series of guidances that provide recommendations for applicants preparing the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD) for submission to the FDA.

²⁵ FDA's guidance for industry on *Changes to an Approved NDA or ANDA*.

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GLOSSARY

Absolute as used to define the acceptable range (+/- 10%) in which individual blend sample values must fall and which is independent of the value of the mean. *For example, if the mean of all blend samples is 95.0%, the absolute range is 85.0% to 105.0%, (not 95.0% +/- 9.5%).*

Exhibit Batches refer to any batch submitted in support of an NDA or ANDA. This includes bioequivalence, test, and commercial production batches of a drug product.

In-process dosage unit is a capsule or tablet as it is formed in the manufacturing process before it is coated or packaged.

RSD is relative standard deviation; $RSD = [(standard\ deviation)/(mean)] \times 100\%$.

Significant event is any operation during solid dosage production process that can affect the integrity of the in-process materials and, hence, their quality attributes. Transferring powder from a blender to a bin or from the bin to a hopper are two examples of significant events in the blending and compression process.

Stratified sampling is the process of collecting a representative sample by selecting units deliberately from various identified locations within a lot or batch, or from various phases or periods of a process. to obtain a Stratified sampling of sample dosage units that specifically targets locations throughout the compression/filling operation that have a higher risk of producing failing results in the finished product uniformity of content; then, random dosage units are selected within these identified locations.

Target assay/Target potency is the intended strength or intended amount of active ingredient in the dosage unit.

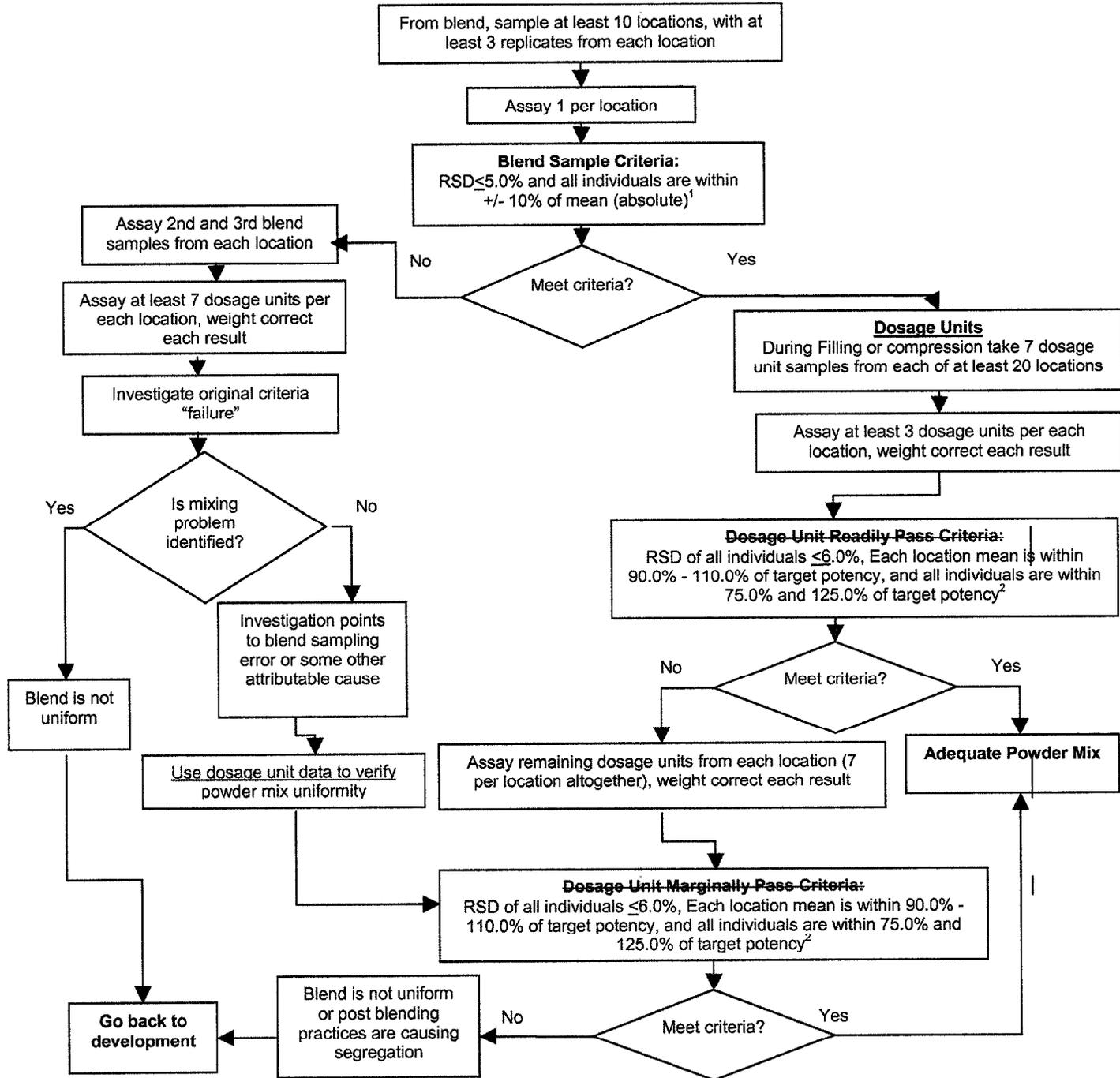
Validation batch is a batch manufactured and tested to verify the proposed routine manufacturing process controls are adequate.

Weight correct is a mathematical correction to eliminate the effect of potentially variable ~~tablet dosage unit~~ weight on measurement of mix adequacy. *For example, a tablet with a strength of 19.4 mg and weight of 98 mg = $19.4 \div 98 = 0.198$ mg/mg. Label claim is 20 mg per each 100 mg tablet, so the weight corrected result is $0.198 \div 0.20 \times 100 = 99\%$ of target blend assay.*

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ATTACHMENT 1: EVALUATION OF EXHIBIT/VALIDATION BATCH POWDER MIX HOMOGENEITY/VERIFICATION OF MANUFACTURING CRITERIA



¹ Examples of "mean +/- 10% (absolute)" are: If the mean strength/potency = 95%, then the interval is 95% +/- 10%; thus, all individuals must fall within 85.0% to 105.0%. If the mean strength/potency = 103.0%, then the interval is 103.0% +/- 10.0%; thus all individuals must fall within 93.0% to 113.0%.

² When comparing individual dosage units to 75.0% - 125.0% of target strength/potency, use the as is results (not corrected for weight).

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ATTACHMENT 2: ROUTINE MANUFACTURING BATCH TESTING

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Before using this chart to demonstrate adequacy of mix and content uniformity during routine manufacture conduct an assessment of the powder mix and compare to, stratified sample correlation data and establishes initial criteria. Identify at least 10 sampling locations during filling or compression to represent the entire batch. Remove 3 or more dosage units at each sampling location.

Use SCM routine criteria if:

1. Validation result was *readily pass* and production is just starting
2. Routine test for previous batch was SCM and it passed SCM criteria
3. Routine test for previous batch was MCM, but switching rule is met

Use MCM routine criteria if:

1. Validation result was *marginally pass* and production is just starting
2. Routine test for previous batch was MCM and it passed MCM criteria
3. Routine test for previous batch started as SCM, but had to switch to MCM to pass

